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(71) Applicant: FORBES MEDI-TECH INC. [CA/CA]; 200-750 West Pender Street, Vancouver, British Columbia V6C 2T8 (CA).

(72) Inventors: MILANOVA, Radka, K.; 605-1749 Robson Street, Vancouver, British Columbia V6G 1E1 (CA). KUTNEY, James, P.; 2118 Nanton Avenue, Vancouver, British Columbia V5L 3C7 (CA). NOVAK, Egon; 11620 Daniels Road, Richmond, British Columbia V6X 3T1 (CA). HOU, Duanjie; 216-2730 Acadia Road, Vancouver, British Columbia V6T 1R9 (CA).

(74) Agent: BEN-OLIEL, Susan, M., M.; 2983 West 41st Avenue, Vancouver, British Columbia V6N 3C8 (CA).

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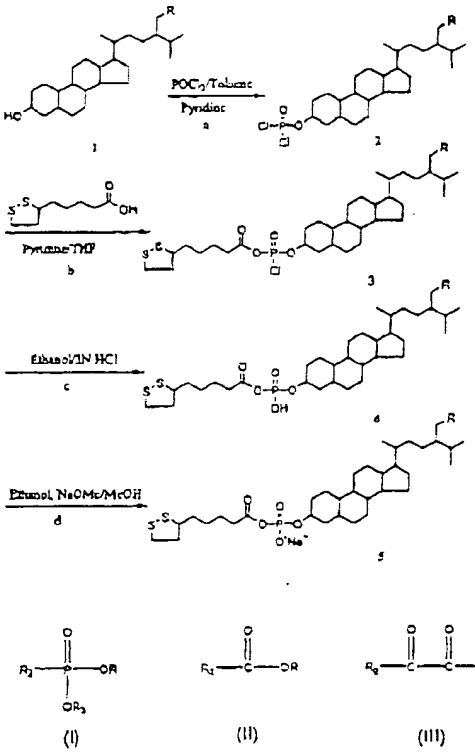
(54) Title: NOVEL DERIVATIVES COMPRISING PHYTOSTEROLS AND/OR PHYTOSTANOLS AND ALPHA-LIPOIC AND USE THEREOF IN TREATING OR PREVENTING CARDIOVASCULAR DISEASE, ITS UNDERLYING CONDITIONS AND OTHER DISORDERS



(57) Abstract: Novel phytosterol and/or phytostanol derivatives, including salts thereof, are represented by general formulae (I), (II), (III) wherein R is a phytosterol or phytostanol moiety, R2 is derived from lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal. These derivatives are effective in treating and preventing cardiovascular disease and its underlying conditions including atherosclerosis and hyperlipidemia.

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TITLE: NOVEL DERIVATIVES COMPRISING PHYTOSTEROLS AND/OR PHYTOSTANOLS AND ALPHA-LIPOIC ACID AND USE THEREOF IN TREATING OR PREVENTING CARDIOVASCULAR DISEASE, ITS UNDERLYING CONDITIONS AND OTHER DISORDERS

FIELD OF THE INVENTION

This present invention relates to the field of phytosterols and phytostanols and their use in treating and preventing cardiovascular disease and other disorders.

BACKGROUND OF THE INVENTION

While recent advances in science and technology are helping to improve quality and add years to human life, the prevention of atherosclerosis, the underlying cause of cardiovascular disease ("CVD") has not been sufficiently addressed. Atherosclerosis is a degenerative process resulting from an interplay of inherited (genetic) factors and environmental factors such as diet and lifestyle. Research to date suggest that cholesterol may play a role in atherosclerosis by forming atherosclerotic plaques in blood vessels, ultimately cutting off blood supply to the heart muscle or alternatively to the brain or limbs, depending on the location of the plaque in the arterial tree (1,2). Overviews have indicated that a 1% reduction in a person's total serum cholesterol yields a 2% reduction in risk of a coronary artery event (3). Statistically, a 10% decrease in average serum cholesterol (e.g. from 6.0 mmol/L to 5.3 mmol/L) may result in the prevention of 100,000 deaths in the United States annually (4).

Sterols are naturally occurring compounds that perform many critical cellular functions. Phytosterols such as campesterol, stigmasterol and beta-sitosterol in plants, ergosterol in fungi and cholesterol in animals are each primary components of cellular and sub-cellular membranes in their respective cell types. The dietary source of phytosterols in humans comes from plant materials i.e. vegetables and plant oils. The

estimated daily phytosterol content in the conventional western-type diet is approximately 60-80 milligrams in contrast to a vegetarian diet which would provide about 500 milligrams per day.

Phytosterols have received a great deal of attention due to their ability to decrease serum cholesterol levels when fed to a number of mammalian species, including humans. While the precise mechanism of action remains largely unknown, the relationship between cholesterol and phytosterols is apparently due in part to the similarities between the respective chemical structures (the differences occurring in the side chains of the molecules). It is assumed that phytosterols displace cholesterol from the micellar phase and thereby reduce its absorption or possibly compete with receptor and/or carrier sites in the cholesterol absorption process.

Over forty years ago, Eli Lilly marketed a sterol preparation from tall oil and later from soybean oil called Cytellin™ which was found to lower serum cholesterol by about 9% according to one report (5). Various subsequent researchers have explored the effects of sitosterol preparations on plasma lipid and lipoprotein concentrations (6) and the effects of sitosterol and campesterol from soybean and tall oil sources on serum cholesterols (7). A composition of phytosterols which has been found to be highly effective in lowering serum cholesterol is disclosed in US Patent Serial No. 5,770,749 to Kutney et al. and comprises no more than 70% by weight beta-sitosterol, at least 10% by weight campesterol and stigmastanol (beta-sitostanol). It is noted in this patent that there is some form of synergy between the constituent phytosterols, affording even better cholesterol-lowering results than had been previously achieved.

Despite the obvious and well recorded advantages of phytosterols in the treatment of a number of disorders, research continues into ways in which the efficacy of phytosterols and their delivery and administration may be improved. For example, the administration of phytosterols and the incorporation thereof into foods, pharmaceuticals and other delivery vehicles has been complicated by the fact that they are highly hydrophobic (i.e. they have poor water solubility). Studies have investigated how the form (for example crystalline, suspension, granular) in which the

phytosterols are dosed impacts on their ability to lower serum cholesterol levels. As phytosterols are highly hydrophobic, they do not dissolve to any appreciable extent in the micellar phase in the digestive tract and therefore are not capable of efficiently blocking cholesterol absorption. Oils and fats are capable to a limited but not satisfactory degree of dissolving free phytosterols. Since only solubilized phytosterols inhibit absorption of cholesterol, adaptations must be made.

Early research focused on grinding or milling the phytosterols in order to enhance their solubility (US Patent Serial Nos: 3,881,005 and 4,195,084 both to Eli Lilly). In addition, researchers have looked to the esterification of phytosterols in order to enhance their solubility. German Patent 2035069/January 28, 1971 (analogous to US Patent No. 3,751,569) describes the addition of phytosterol fatty acid esters to cooking oil. The esterification is carried out between a free sterol and a fatty acid anhydride, with perchloric acid as the catalyst. The significant drawback to this process, along with others, is the use of non-food grade catalysts and reagents.

US Patent Serial no. 4,588,717 to the David E. Mitchell Medical Research Institiute describes a vitamin supplement which comprises a fatty acid ester of a phytosterol, wherein the fatty acid ester has from about 18 to 20 carbon atoms in the main carbon chain.

US Patent Serial No. 5,502,045 to Raision Tehtaat Oy AB describes the preparation of a beta-sitostanol fatty acid ester mixture. Although the attempt of this patent is to produce a soluble and stable phytostanol delivery system, there are some problems with the long term stability of these "fatty acid" esterified products due to the ultimate oxidation of the unsaturated fatty acid moiety.

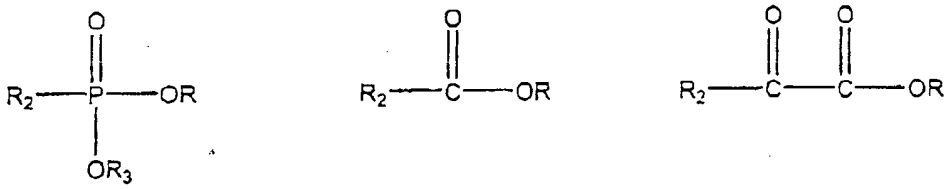
Accordingly, the provision of a stable oil-soluble phytosterol/phytostanol derivative which could be administered orally and which could be incorporated without further modification into delivery vehicles would be highly desirable and has not heretofore been satisfactorily achieved.

It is an object of the present invention to obviate or mitigate the above disadvantages.

SUMMARY OF THE INVENTION

The present invention provides, in one aspect, a composition comprising one or more of the following:

a) a derivative represented by one or more of the general formulae:



I II III

wherein R is a phytosterol or phytostanol moiety; R2 is derived from lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal;

b) a phytosterol and/or phytostanol in combination with lipoic acid or analogues thereof; and

c) salts of either a) or b).

The present invention further provides for the use of the composition, defined above, for treating or preventing CVD and its underlying conditions including atherosclerosis, hypercholesterolemia, hyperlipidemia, hypertension, thrombosis, and related diseases such as Type II diabetes, as well as other diseases that include oxidative damage as

part of the underlying disease process such as dementia, Alzheimer's disease, aging, and cancer.

The present invention further provides foods, beverages and nutraceuticals supplemented with the composition as defined above.

The present invention further provides a method for treating or preventing CVD and its underlying conditions including atherosclerosis, hypercholesterolemia, hyperlipidemia, hypertension, thrombosis, and related diseases such as Type II diabetes, as well as other diseases that include oxidative damage as part of the underlying disease process such as dementia, aging, and cancer by administering to a human or animal the composition as defined herein.

The present invention also comprises processes of preparing the novel composition as defined above.

The composition of the present invention is based on the heretofore, uninvestigated benefit of "combining" phytosterols and/or phytostanols with lipoic acid. Within the scope of the present invention, this "combination" is achieved two ways: through the formation of a derivative (a new chemical structure) having one of the following general formulae:

wherein R is a phytosterol or phytostanol moiety; R2 is derived from lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal; or through the physical mixing of the two constituent moieties, phytosterols and lipoic acid or their salts.

The compositions of the present invention have numerous advantages over the phytosterol/stanol compositions previously known and described in the art. In particular, what is primarily achieved is enhanced solubility of the phytosterol/stanol constituents in oils and fats, without the need for other structural modifications to the

sterols and stanols. Not only does this facilitate the incorporation of sterols and stanols into "delivery" vehicles (with the attendant cost and time savings) but this composition is more readily absorbed in bile acid micelli, thereby efficiently displacing cholesterol and blocking its absorption. Both phytosterols and phytostanols must first be dissolved in oil micelles in the intestine before interaction with cholesterol can occur. Accordingly, compositions of the present invention can be prepared and used as such or they can be easily incorporated into foods, beverages, pharmaceuticals and nutraceuticals regardless of whether these "vehicles" are oil-based. This enhanced solubility generally translates into lower administration dosages of the phytosterol/phytostanol and lipoic acid moieties in order to achieve the desired therapeutic effect.

A second advantage of the compositions of the present invention is that there may be an additive or synergistic therapeutic effect, both in lowering serum cholesterol and as an anti-oxidant, between the phytosterol/stanol component and the lipoic acid. These effects and other significant advantages are described in more detail below.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art from the following detailed description. It is to be understood, however, that the detailed description and examples, while indicating preferred embodiments of the present invention, are given by way of illustration and not by limitation. Many changes and modifications within the scope of the present invention can be made without departing from the spirit thereof, and the invention includes all such modifications.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is illustrated by way the following non-limiting drawings in which:

Figure 1 is a schematic showing a process of preparing phytostanol-phosphate-lipoate;

Figure 2 is a schematic showing a process of preparing phytostanol-oxalate-lipoate;

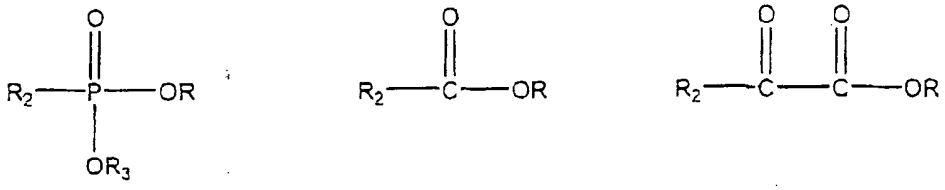
and

Figure 3 is a schematic showing a process of preparing phytostanol-lipoate.

PREFERRED EMBODIMENTS OF THE INVENTION

According to one aspect of the present invention, there is provided a novel composition comprising one or more of the following:

a) a derivative represented by one or more of the general formulae:



I II III

wherein R is a phytosterol or phytostanol moiety; R2 is derived from lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal;

b) a phytosterol and/or phytostanol in combination with lipoic acid or analogues thereof; and

c) salts of either a) or b).

These compositions are suitable for use in human and animals for treating or preventing CVD and its underlying conditions, such as atherosclerosis, hypercholesterolemia, hyperlipidemia, hypertension, thrombosis, and related diseases such as Type II diabetes, as well as in treating and preventing other diseases that include oxidative damage as part of the underlying disease process such as dementia,

Alzheimer's disease, aging, and cancer. The components of the composition will be described in more detail below. It should be noted that, throughout this disclosure, the terms "derivative", "structure" and "analogue" are used interchangeably to describe the novel unitary compound which links both a phytosterol or phytostanol and lipoic acid and described at a) above.

Phytosterols/Phytostanols

As used herein, the term "phytosterol" includes all phytosterols without limitation, for example: sitosterol, campesterol, stigmasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol and all natural or synthesized forms and derivatives thereof, including isomers. The term "phytostanol" includes all saturated or hydrogenated phytosterols and all natural or synthesized forms and derivatives thereof, including isomers. It is to be understood that modifications to the phytosterols and phytostanols i.e. to include side chains also falls within the purview of this invention. It is also to be understood that, when in doubt throughout the specification, the term "phytosterol" encompasses both phytosterol and phytostanol i.e. the terms may be used interchangeably unless otherwise specified.

The phytosterols and phytostanols for use in forming compositions in accordance with this invention may be procured from a variety of natural sources. For example, they may be obtained from the processing of plant oils (including aquatic plants) such as corn oil and other vegetable oils, wheat germ oil, soy extract, rice extract, rice bran, rapeseed oil, sunflower oil, sesame oil and fish (and other marine-source) oils. The present invention is not to be limited to any one source of phytsterols. US Patent Serial No. 4,420,427 teaches the preparation of sterols from vegetable oil sludge using solvents such as methanol. Alternatively, phytosterols and phytostanols may be obtained from tall oil pitch or soap, by-products of forestry practises as described in US Patent Serial No.5,770,749, incorporated herein by reference.

In one preferred form, the composition of the present invention is formed with naturally-derived or synthesized beta-sitosterol, campestanol, sitostanol and campesterol. In another preferred form, the composition of the present invention is

formed with naturally-derived or synthesized sitostanol or with naturally derived or synthesized campestanol or mixtures thereof.

Lipoic Acid

Alpha-lipoic acid is chemically referred to 1,2-dithiolane-3-pentanoic acid, 5-(1,2-dithiolane-3-yl)-valeric acid or 5,3-(1,2-dithioanyl)pentanoic acid. Alpha-lipoic acid possesses a chiral C atom, occurs in two enantiomeric forms and is found physiologically in plants, in bacteria and in mammals. It functions as an essential co-factor in metabolic reactions involved in energy utilization (8). Research in muscle and fat cells has demonstrated that alpha-lipoic acid stimulates glucose transport and has a positive effect on insulin-stimulated glucose up-take (9). Alpha-lipoic acid and its reduced form, dihydrolipoic acid, may also have effects on genes and regulatory proteins involved in normal growth and metabolism (10).

Alpha-lipoic acid and dihydrolipoic acid are both effective as fat and water-soluble anti-oxidants. Alpha-lipoic acid is readily absorbed, transported and taken up by cells where it is reduced in various tissues, including the brain (11). It has been found to scavenge free hydroxyl radicals, singlet oxygen, hydrogen peroxide, hypochlorous acid, peroxynitrite and nitric oxide and may also exert an anti-oxidant effect through the chelation of copper, iron and other transition metals (10,12,13). In animal studies, alpha-lipoic acid supplementation prevented symptoms of vitamin C and E deficiency indicating a synergy between alpha-lipoic acid and other anti-oxidants (14,15). Additionally, alpha-lipoic acid supplementaion has been shown to increase the intracellular levels of the anti-oxidant enzyme glutathione by 30-70% (16).

R2 comprises lipoic acid or any derivative thereof. What is achieved within the scope of the present invention is the creation of a new structure or compound wherein a phytosterol or phytostanol moiety is chemically linked to lipoic acid. The union benefits and enhances the both parts of this new structure. The phytosterol moiety, formerly poorly soluble, becomes, as part of the new derivative, much more readily soluble in

aqueous and non-aqueous media such as oils and fats. Accordingly, administration of the phytosterol becomes possible without any further enhancements to modify its delivery.

Derivative Formation

a) Ester Formation

There are many processes by which novel structures comprising phytosterols and/or phytostanols and lipoic acid can be formed. In general, the selected phytosterol or stanol (or halophosphate, halocarbonate or halo-oxalate derivatives thereof) and lipoic acid are mixed together under reaction conditions to permit condensation of the "acid" moiety with the "alcohol" (phytosterol). These conditions are the same as those used in other common esterification reactions such as the Fisher esterification process in which the acid component and the alcohol component are allowed to react directly or in the presence of a suitable acid catalyst such as mineral acid, sulfuric acid, phosphoric acid, p-toluenesulfonic acid. The organic solvents generally employed in such esterification reactions are ethers such as diethyl ether, tetrahydrofuran, or benzene, toluene or similar aromatic solvents and the temperatures can vary from room to elevated temperatures depending on the reactivity of the reactants undergoing the reaction.

In a preferred embodiment, the process to form the ester derivative comprises condensing lipoic acid with the phytosterol/phytostanol or its' halophosphate, halocarbonate or halo-oxalate under suitable reaction conditions. In general, such condensation reactions are conducted in an organic solvent such as diethyl ether, tetrahydrofuran, or benzene, toluene or similar aromatic solvents. Depending on the nature and reactivity of the reactants, the reaction temperatures may vary from low (-15°C) to room to elevated temperatures.

Figure 1 is a schematic showing the formation of a chlorophosphate/stanol derivative

(step a), and the condensation reaction yielding one of novel derivatives of the present invention based on formula I: phytostanol-phosphate-lipoate (noted as structure 4).

In more detail, the process shown in Figure 1 is as follows: phytostanol chlorophosphate (structure 2) is prepared by forming a solution of phytostanol in toluene and pyridine (although other nitrogen bases such as aliphatic and aromatic amines may alternatively be used) and treating this solution with a phosphorus derivative such as phosphorus oxychloride. The residue so formed after filtration and concentration of the mother liquor is phytostanol chlorophosphate (structure 3). The latter is then mixed with lipoic acid and, after the addition of a suitable alcohol such as ethanol and HCl (step c), concentrated. Altematively, pyridine/THF may be added and the product concentrated. After final washing and drying, the resultant novel product is phytostanol-phosphate-lipoate (structure 6).

Figure 2 is a schematic showing the formation of the intermediary chloro-oxalate/stanol derivative (step a), and the condensation reaction (step b) yielding a novel structure 7, one of novel derivatives of the present invention based on formula III: phytostanol-oxalate-lipoate. These chloro-oxalate derivatives may be prepared by the same process outlined in detail above with respect to Figure 1; however, the phosphorus oxylchloride is replaced by oxalyl chloride.

Figure 3 is a schematic showing the formation of one of the novel derivatives of the present invention based on formula II: phytostanol-lipoate, shown as structure 8.

b) Salt Formation

The present invention encompasses not only the parent structures comprising phytosterols or phytostanols and lipoic acid (for example, those preferred structures shown as structures 4, 7 and 8 in the Figures but also the salts thereof. These salts are even more water soluble than the corresponding parent compounds and therefore their efficacy and evaluation both *in vitro* and *in vivo* is much improved.

Salt formation of the derivatives of the present invention can be readily performed by treatment of the parent compound with a series of bases (for example, sodium methoxide or other metal alkoxides) to produce the corresponding alkali metal salts. Other metal salts of calcium, magnesium, manganese, copper, zinc, and the like can be generated by reacting the parent with suitable metal alkoxides. With respect to formula I, R3 represents either hydrogen (parent compound) or any metal, alkali earth metal, or alkali metal (the salt).

c) Reduction by Catalytic (Hydrogenation) and Chemical Methods

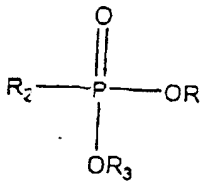
Optionally, the phytosterol derivatives of the present invention or the constituent moieties thereof (either the phytosterol or the lipoic acid) prior to or after derivative formation may be hydrogenated or saturated. The hydrogenation of heterocyclic ring systems to the partially or fully reduced analogues is a well known process. For example, the catalytic and/or chemical reduction of the ring of lipoic acid to the corresponding dihydro analogue is readily accomplished under an atmosphere of hydrogen and a metal catalyst such as platinum, palladium or Raney Nickel. In general, this reduction is performed in an organic solvent such as ethanol, ethyl acetate or similar media and either under atmospheric pressure or at a low pressure (3-5 psi) at room temperature or slightly elevated temperatures.

The chemical reductions of such systems involve reduction with a family of "hydride" reagents such as sodium borohydride, lithium aluminum hydride and their analogues. These reductions are generally performed in an anhydrous inert medium involving ethyl ether, tetrahydrofuran, dioxane, or benzene, toluene or similar aromatic solvents at room to reflux temperatures.

Similar catalytic or chemical processes can be applied to all of the phytosterol analogues of the present invention. Accordingly, the present invention includes within its scope all fully or partially reduced derivatives wherein the lipoic acid is partially or fully reduced and/or wherein the phytosterol moiety is fully or partially hydrogenated.

Derivatives

The present invention comprises all derivatives comprising phytosterol and/or phytostanol and lipoic acid, including salts thereof represented by the general formulae:



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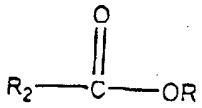
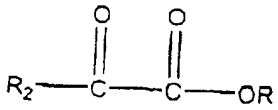


II



III

wherein R is a phytosterol or phytostanol moiety; R2 is derived from lipoic acid and R3

is hydrogen or any metal, alkali earth metal, or alkali metal. Most preferably, the present invention comprises all halophosphate, halocarbonate and halo-oxalate/phytostanol/lipoate derivatives as shown in the Figures as structures 4, 7, and 8. It is to be clearly understood; however, that these structures are only a selection of the many novel derivatives which fall within the purview of formulae I, II and III. It is also to be understood that although a sodium salt is shown as structure 5 in Figure 1, other salts are included within the scope of the invention, as described above.

Potential Advantages of Novel Phytosterol Compositions

The novel derivatives of the present invention, wherein lipoic acid is attached to the phytosterol moiety affords many dietary and therapeutic advantages when compared to the use of phytosterols/phytostanols without such attachment. First and foremost, solubility of the novel derivatives is greatly enhanced, both in aqueous solutions and non-aqueous media such as oils and fats. With this greater solubility, effective dietary and therapeutic dosages and concomitantly costs, can be reduced. Secondly, it is very likely that there is a synergistic or additive effect between the phytosterol moiety and the lipoic acid, when united in one structure, in treating or preventing not only cardiovascular disease and its underlying conditions including atherosclerosis and hyperlipidemia but also diseases that have oxidative damage in their pathology such as cancer, aging, demetia and Alzheimer's. Thirdly, the formation of these derivatives allows the full potential of lipoic acid to be realized while eliminating decomposition. Fourthly, these derivatives are heat stable (stable to oxidation and hydrolysis) which is essential for further processing in, for example, extruders and food processors.

Non-Structural Linkages between Phytosterols and Alpha-Lipoic Acid: Admixtures

Within the scope of the present invention are compositions comprising one or more phytosterols and or phytostanols in combination with lipoic acid or analogues thereof. In other words, this embodiment encompasses the physical admixing of the ingredients without the necessity of forming a new chemical structure.

In a preferred form of this composition, there is additionally provided one or more omega-3 polyunsaturated fatty acids ("PUFA's") admixed with the sterol/stanol component and the alpha-lipoic acid component.

Omega-3 PUFAs

The most preferred omega-3 PUFAs for use within the composition of the present invention are selected from alpha-linolenic acid, eicosapentaenoic acid ("EPA") and docohexaenoic acid ("DHA") in the form of, inter alia, fatty acids, triglycerides,

phospholipids, esters or free fatty acid salts. In one embodiment of the present invention, the omega-3 PUFAs may be extracted from zooplankton, fish or other marine animals using suitable bioconcentration techniques. In the alternative, omega-3 PUFAs may be synthesized using microalgae as the source material. In one preferred form, marine fish oil may be mixed directly with the phytosterol and/or stanol components to form the composition of the present invention. The marine oil may be extracted by techniques known in the art from, inter alia: finfish such as cod, salmon, tuna, herring, halibut, shark, catfish, pollock, dogfish, anchovy, mackerel, trout, and eel; animals such as seals and whales; crustaceans such as crabs, clams and lobster; mollusks and the like.

Without limiting the generality of the foregoing, the most preferred marine sources of omega-3 PUFAs are as follows:

Source	Grams, Omega-3/100 calories*
fish oil capsules	2.86
salmon (sockeye)	1.71
tuna	1.22
salmon (pink)	1.15
shark (spiny dogfish	1.14
halibut	1.13
anchovy	1.10
salmon (Atlantic)	1.08
mackerel (Atlantic)	1.08
salmon (Pacific)	1.03
spanish sardine	0.91
trout (rainbow)	0.86
mackerel (Pacific)	0.85
swordfish (herring)	0.75

(41)

Alternatively, plant sources of omega-3 PUFAs may be used. The great advantage of plant sources is reduced odour as compared to some marine sources. Plant sources include, but are not limited to, plant oils such as hemp oil, flax seed oil and corn oil as well as soy.

The composition of phytosterols and/or phytostanols, alpha-lipoic aicd and omega-3 PUFA may be combined in any of the various conventional pharmaceutical preparations and dosage forms described below. In a most preferred form, the components are combined in a capsule. Preferred concentration ranges, for most dosage forms, including the capsule form are:

Phytosterols/Phytostanols: 100-525mg (with a most preferred target dosage of 300mg)
Omega-PUFAs : 100-525 mg (with a most preferred target dosage of 300mg) Alpha-Lipoic Acid: 5-300mg

In capsule form as shown above, it is preferred that a total of three (3) capsules be administered per day with each meal for optimal therapeutic efficacy.

Other capsule fill excipients may include the following: emulsifiers/surfactants (such as lecithin, polysorbate 80, etc); suspending agents (such as beeswax, hydrogenated vegetable oils, etc); diluent (such as soybean oil, etc) and other anti-oxidants such as alpha-tocopherol.

In the case of softgel capsule formulation, the outer layer may include one or more of the following: softgel base ingredients (such as gelatin, non-bovine), plasticisers (such as glycerol), solvents for gelatin (such as water), and approved shell coloring agents (such as titanium dioxide for a white opaque capsule).

The combination of omega PUFAs with phytosterols and alpha-lipoic acid achieves a number of unexpected therapeutic benefits. Without being bound to any one theory of the inter-relation of these components, several effects are apparent. Alpha-lipoic acid, as noted above, enhances the solubility of phytosterols and phytostanols in fats and oils. Alpha-lipoic acid is also an effective anti-oxidant. Omega-3 PUFA's, although effective in lowering serum triglycerides ("TG") have the troublesome side-effect of often increasing serum levels of low density lipoprotein cholesterol (LDL-C). Conversely, phytosterols while known for their beneficial LDL-C lowering effect may increase serum TG levels under some conditions. It is possible that the beneficial "synergisitic" effects of the composition described herein in lowering both serum LDL-C and TG is the result of each component "optimizing the effects of the other two. For example, omega-3 PUFA may serve to provide the lipid component needed for optimal activity of phytosterols in lowering cholesterol, may counteract the TG effect and while being at risk itself for oxidation, may benefit from the strong anti-oxidant effect of alpha-lipoic acid.

Delivery Systems

Although it is fully contemplated within the scope of the present invention that the derivatives may be administered to animals, particularly humans, directly and without any further modification, it is possible to take further steps to enhance delivery and ensure even distribution throughout the food, beverage, pharmaceutical, nutraceutical and the like to which they are added. It is to be understood; however, that these steps are purely optional. Such enhancement may be achieved by a number of suitable means such as, for example, solubilizing or dispersing the derivatives to form emulsions, solutions and dispersions or self-emulsifying systems; lyophilizing, spray drying, controlled precipitating, or a combination thereof; forming solid dispersions, suspensions, hydrated lipid systems; forming inclusion complexations with cyclodextrins; and using hydrotopes and formulations with bile acids and their derivatives. All of these techniques are described in PCT/CA99/00512, which was published on December 16, 1999 (the contents of which are incorporated herein by reference).

Methods of Use

The compositions and derivatives of the present invention may be used directly and without further modification in cooking, baking and the like as agents to lower serum cholesterol in animals, particularly humans. They may be added to any edible oil and used for cooking, baking, and general use. Alternatively, they may be treated to enhance delivery into various other delivery media.

In addition, the present invention fully contemplates the formation of oleaginous gel foodstuffs such as peanut butter, mayonnaise, ice cream and margarine spreads incorporating such structures. Further, the compositions can readily be included in a variety of low fat foods such as yoghurts. There are numerous modes or "vehicles" of delivery of the composition , accordingly, this invention is not intended to be limited to the following delivery examples.

1) Pharmaceutical Dosage Forms:

It is contemplated within the scope of the present invention that the compositions of the present invention may be incorporated into various conventional pharmaceutical preparations and dosage forms such as tablets (plain and coated) for use orally, bucally or lingually, capsules (hard and soft, gelatin, with or without additional coatings) powders, granules (including effervescent granules), pellets, microparticulates, solutions (such as micellar, syrups, elixirs and drops), lozenges, pastilles, ampuls, emulsions, microemulsions, ointments, creams, suppositories, gels, and transdermal patches, modified release dosage forms together with customary excipients and/or diluents and stabilizers.

The compositions of the present invention, adapted into the appropriate dosage form as described above may be administered to animals, including humans, orally, by injection (intra-venously, subcutaneously, intra-peritoneally, intra-dermally or intra-muscularly), topically or in other ways. Although the precise mechanism of action is unclear, the compositions of the present invention, administered intra-venously, lower serum cholesterol. It is believed that some blends of phytosterols, in concert,

may have, in addition to the role as an inhibitor of cholesterol absorption in the intestine, a systemic effect on cholesterol homeostasis through bile acid synthesis, enterocycte and biliary cholesterol excretion, bile acid excretion and changes in enzyme kinetics and cholesterol transport between various compartments within the body (PCT/CA97/00474 which was published on January 15, 1998).

The compositions, as described herein, may be used in both dietary and therapeutic capacities in order to treat and/or prevent CVD, its underlying conditions such as hypercholesterolemia, hyperlipidemia, arteriosclerosis, hypertension, thrombosis, related diseases such as Type II diabetes, as well as other diseases that include oxidative damage as part of the underlying disease process such as dementia, aging, and cancer. In populations, which are considered "high-risk" for CVD or any of the oxidation related disorders, it is contemplated that the vehicles and foodstuffs in which they are contained be used in primary, secondary and tertiary treatment programs.

In order to appreciate the various possible vehicles of the delivery of the compositions, the list below is provided. The doses will vary depending upon, among other factors, the mode of delivery (i.e. how and into which food or beverage or pharmaceutical the phytosterol/stanol derivatives are ultimately incorporated), the patient size and condition, the result to be achieved, as well as other factors known to those skilled in the art of food additives and medicinal agents. Generally, however, it is preferred that the derivatives of the present invention be administered to humans in a form comprising up to 6 grams (based on a 70kg person) of phytosterols and/or phytostanols per day, more preferably from 1-5 grams per day and most preferably 1.5 grams per day. It will also be recognized that the provision of much larger daily doses of the derivatives are not harmful to the animal host, as excess will simply pass through normal excretory channels.

2) Foods/Beverages/Nutraceuticals:

In another form of the present invention, the compositions of the present invention

may be incorporated into foods, beverages and nutraceuticals, including, without limitation, the following:

1) Dairy Products –such as cheeses, butter, milk and other dairy beverages, spreads and dairy mixes, ice cream and yoghurt;

2) Fat-Based Products--such as margarines, spreads, mayonnaise, shortenings, cooking and frying oils and dressings;

3) Cereal-Based Products–comprising grains (for example, bread and pastas) whether these goods are cooked, baked or otherwise processed;

4) Confectioneries--such as chocolate, candies, chewing gum, desserts, non-dairy toppings (for example Cool Whip™), sorbets, icings and other fillings;

5) Beverages– whether alcoholic or non-alcoholic and including colas and other soft drinks, juice drinks, dietary supplement and meal replacement drinks such as those sold under the trade-marks Boost™ and Ensure™; and

1) Miscellaneous Products–including eggs and egg products, processed foods such as soups, pre-prepared pastas

The compositions of the present invention may be incorporated directly and without further modification into foods, nutraceuticals or beverages by techniques such as mixing, infusion, injection, blending, dispersing, emulsifying, immersion, spraying and kneading. Alternatively, the compositions may be applied directly onto a food or into a beverage by the consumer prior to ingestion. These are simple and economical modes of delivery.

While the following examples are intended to illustrate various aspects of the present invention and to assist in the preparation of the compositions and derivatives, they are not intended to limit the scope of invention as claimed herein.

EXAMPLES

The present invention is described by the following non-limiting examples:

EXAMPLE 1 Formation Phytosterol/Lipoic Acid Derivative

1. To an dry 1 L round bottom flask equipped with a Dean-Stark trap and a water condenser, phytostanols (15.22 g, 0.037 mol), α-lipoic acid (9.16 g, 0.044 mol) and toluene (505 ml) were added.
2. The mixture was stirred at room temperature for 5 min, then *p*-TSA (1.75g, 9.0 mmol) was added.
3. The reaction mixture was heated to reflux.
4. During this time, the reaction was monitored by TLC (mobil phase: hexanes/EtOAc = 3/1).
5. After 4.75 h reflux a second portion of *p*-TSA (180 mg, 0.93 mmol) and α-lipoic acid (0.920 g, 4.5 mmol) were added and the mixture was continuesly refluxed for additional 2 h.
6. Toluene (200 ml) was added and the mixture was washed with water (125 ml), aqueous solution of $NaHCO_3$ (3 x 125 ml) and water (3 x 125 ml).
7. The extract was dried over Na_2SO_4, concentrated on a rotary evaporator to give a light yellow residue.
9. The residue was purified by recrystalization with methanol (100 ml) under heating to yield phytostanol lipoate (21.25 g, yield 95.8%).

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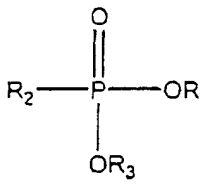
WE CLAIM:

1. A composition comprising one or more of the following:

a) a derivative represented by one or more of the general formulae:



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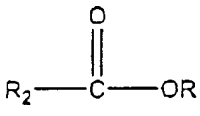

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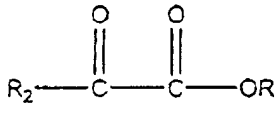


III

wherein R is a phytosterol or phytostanol moiety; R2 is derived from alpha-lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal;

b) a phytosterol and/or phytostanol in combination with lipoic acid or analogues thereof; and

c) salts of either a) or b).

2. The composition of claim 1 wherein the phytosterol is selected from the group consisting of sitosterol, campesterol, stigmasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol and all natural or synthesized forms and derivatives thereof, including isomers.

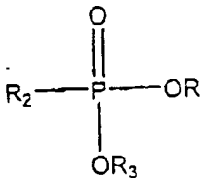
3. The composition of claim 1 wherein the phytostanol is selected from the group consisting of all saturated or hydrogenated phytosterols and all natural or synthesized forms and derivatives thereof, including isomers.

4. The composition of claim 1 wherein the phytostanol is sitostanol.

5. The composition of claim 1 wherein R3 is selected from the group consisting of calcium, magnesium, manganese, copper, zinc, sodium, potassium and lithium.

6. A method of treating or preventing cardiovascular disease and its underlying conditions, including atherosclerosis and hypercholesterolemia, in an animal which comprises administering to the animal a composition comprising one or more of the following:

a) a derivative represented by one or more of the general formulae:



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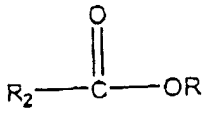
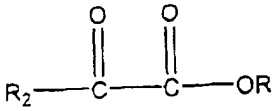


II



III

wherein R is a phytosterol or phytostanol moiety; R2 is derived from alpha-lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal;

b) a phytosterol and/or phytostanol in combination with lipoic acid or analogues thereof; and

c) salts of either a) or b).

7. The method of claim 6 wherein the animal is human.

8. The method of claim 6 wherein the phytosterol is selected from the group consisting of sitosterol, campesterol, stigmasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol and all natural or synthesized forms and derivatives thereof, including isomers.

9. The method of claim 6 wherein the phytostanol is selected from the group consisting of all saturated or hydrogenated phytosterols and all natural or synthesized forms and derivatives thereof, including isomers.

10. The method of claim 6 wherein the phytostanol is sitostanol.

11. The method of claim 6 wherein R3 is selected from the group consisting of calcium, magnesium, manganese, copper, zinc, sodium, potassium and lithium.

12. The method of claim 6 wherein the composition is administered in an amount sufficient to deliver to the animal from 1 to 10 grams of phytosterols per day.

13. A food product which comprises the composition of claim 1.

14. A beverage which comprises the composition of claim 1.

15. A pharmaceutically acceptable formulation comprising the composition of claim 1 and an adjuvant or carrier therefor.

16. A composition comprising at least one phytosterol and/or phytostanol, at least one derivative of alpha-lipoic acid and at least one omega-3 polyunsaturated fatty acid.

17. The composition of claim 16 additionally comprising a pharmaceutically acceptable

carrier material.

Figure 1

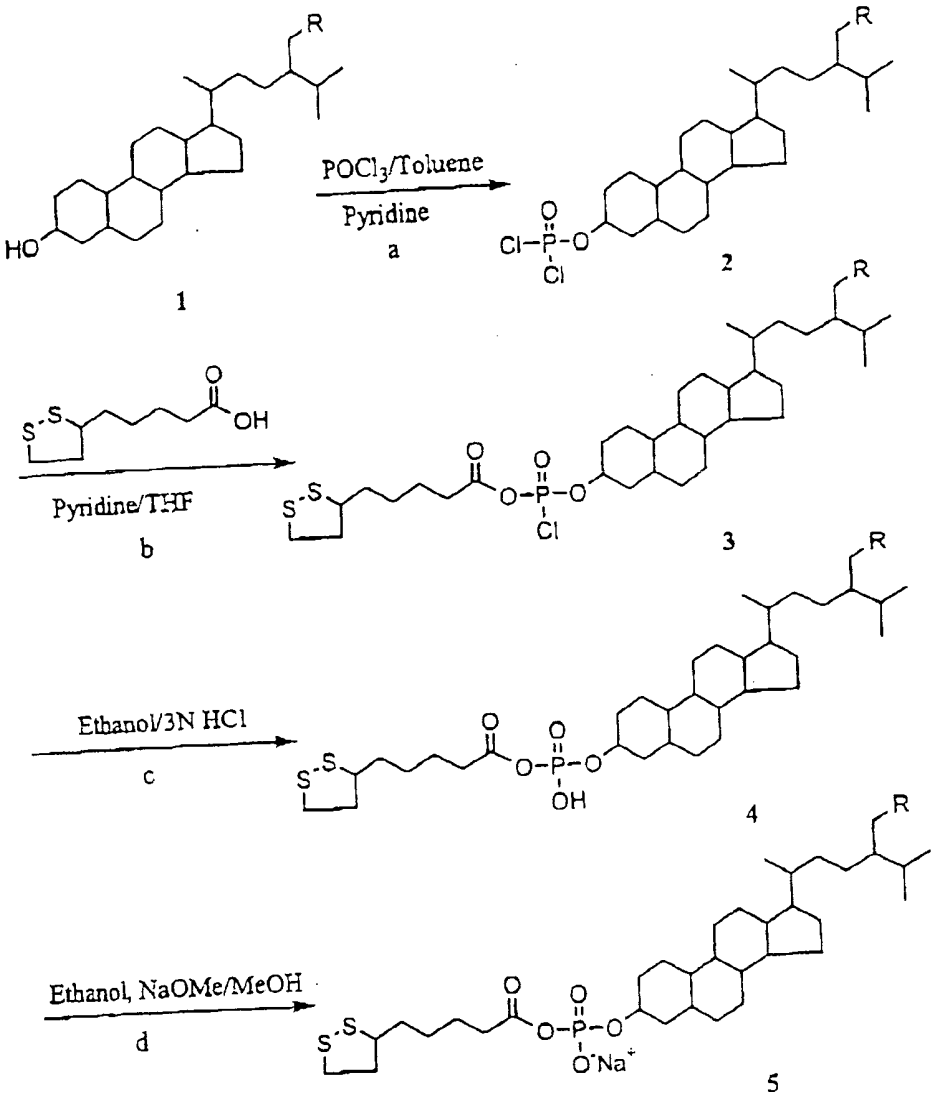

R
HO
1
POCl3/Toluene
Pyridine
a
Cl–P–O
Cl
2
O
S
S
OH
Pyridine/THF
b
3
Ethanol/3N HCl
c
OH
4
Ethanol, NaOMe/MeOH
d
O⁻Na⁺
5

Figure 2

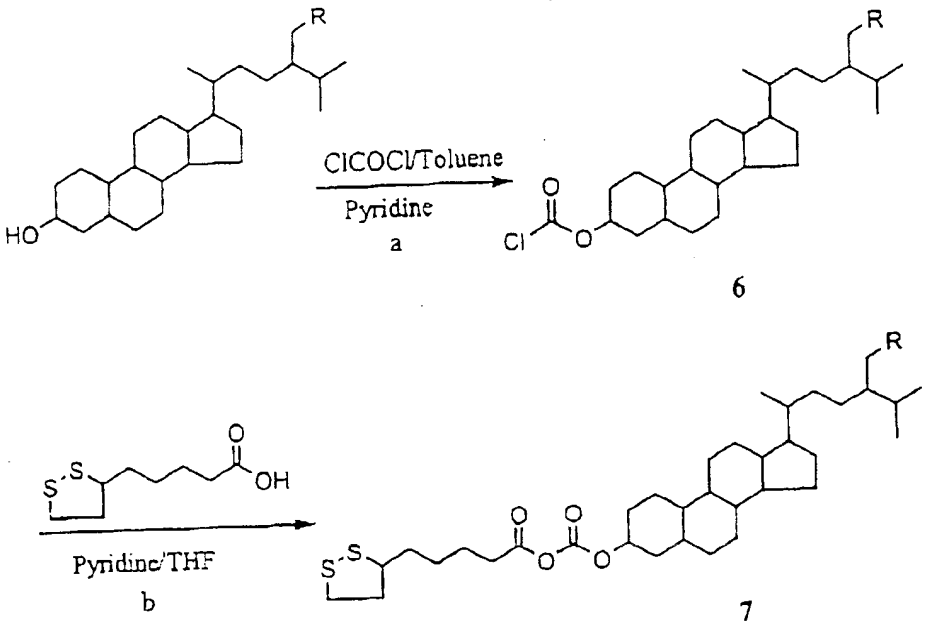
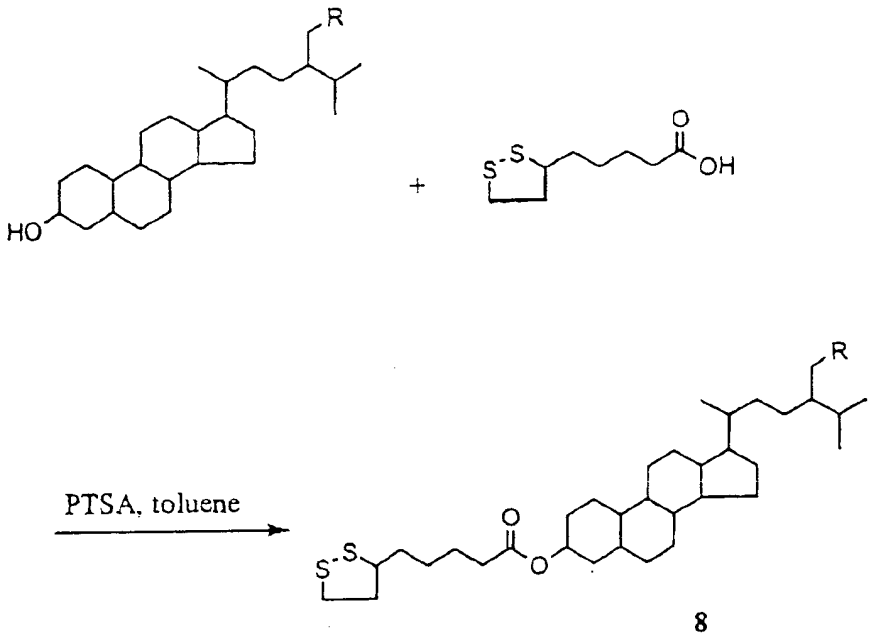


Figure 3



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(71) Applicant: FORBES MEDI-TECH INC. [CA/CA]; 200-750 West Pender Street, Vancouver, British Columbia V6C 2T8 (CA).

(72) Inventors: MILANOVA, Radka, K.; 605-1749 Robson Street, Vancouver, British Columbia V6G 1E1 (CA). KUTNEY, James, P.; 2118 Nanton Avenue, Vancouver, British Columbia V6L 3C7 (CA). NOVAK, Egon; 11620 Daniels Road, Richmond, British Columbia V6X 3T1 (CA). HOU, Duanjie; 216-2730 Acadia Road, Vancouver, British Columbia V6T 1R9 (CA).

(74) Agent: BEN-OLIEL, Susan, M, M.; 2983 West 41st Avenue, Vancouver, British Columbia V6N 3C8 (CA).

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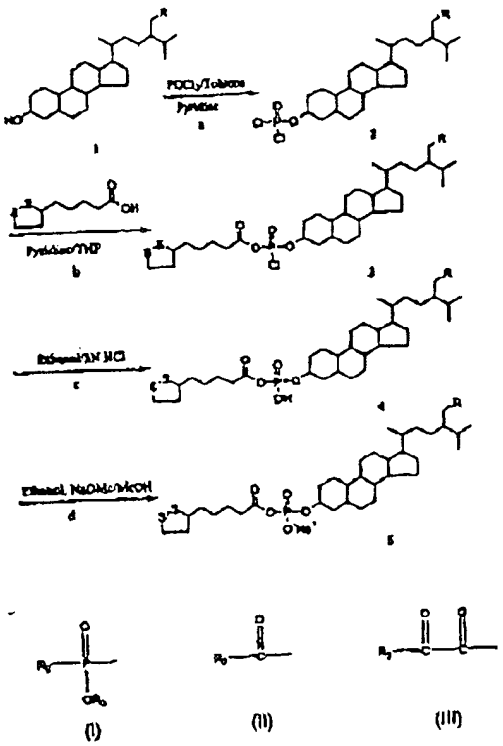
[Continued on next page]

(54) Title: NOVEL DERIVATIVES COMPRISING PHYTOSTEROLS AND/OR PHYTOSTANOLS AND ALPHA-LIPOIC AND USE THEREOF IN TREATING OR PREVENTING CARDIOVASCULAR DISEASE, ITS UNDERLYING CONDITIONS AND OTHER DISORDERS



(I) (II) (III)

(57) Abstract: Novel phytosterol and/or phytostanol derivatives, including salts thereof, are represented by general formulae (I), (II), (III) wherein R is a phytosterol or phytostanol moiety, R2 is derived from lipoic acid and R3 is hydrogen or any metal, alkali earth metal, or alkali metal. These derivatives are effective in treating and preventing cardiovascular disease and its underlying conditions including atherosclerosis and hyperlipidemia.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/58 A61K31/661 A61P9/00 A61P9/10 A61P3/06
A23L1/30 A61K31/66 A61K31/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP 0 436 936 A (HOECHST AG) 17 July 1991 (1991-07-17) abstract page 2, line 11 -page 4, line 50 page 9, line 45 -page 10, line 15 page 10, line 31 -page 11, line 53 page 23, line 45 -page 24, line 14 page 25, line 15 - line 35 example 53; table 3 example 46; table 5 page 41, line 13 - line 25 claims 1-3,7,8,11-15 ---	1,6,7, 12,13,15 2-5, 8-11,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2001	16/11/2001

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00285

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 00 843 A (MARIGEN SA) 20 July 1995 (1995-07-20)	1
A	abstract page 2, line 5 -page 3, line 49 page 4, line 9 - line 22 page 4, line 36 - line 44 page 6, line 1 - line 9 page 8, line 51 -page 9, line 7 page 14, line 26 - line 34 claims	2-14
X	WO 98 33494 A (KOSBAB JOHN V) 6 August 1998 (1998-08-06) abstract page 2, line 10 - line 19 page 3, line 10 - line 17 page 12, line 27 -page 13, line 12 page 13, line 20 page 15, line 5 - line 20 page 20, line 9 - line 14 page 21, line 24 - line 30 page 24, line 31 - line 37 page 32, line 29 -page 33, line 18 page 34, line 20 - line 32 page 38, line 19 - line 24 table 4	1,2,6-8, 15-17
X	WO 99 57246 A (LIFE TECHNOLOGIES INC) 11 November 1999 (1999-11-11) abstract page 6, line 10 - line 18 page 11, line 1 - line 12 page 14; table 1 page 17, line 1 - line 7 page 18, line 11 - line 30 claims 2,5,10,11	1-3
A	WO 99 11144 A (RICEX COMPANY INC ;LYNCH IKE E (US); MCPEAK PATRICIA (US); CHERUKU) 11 March 1999 (1999-03-11) abstract page 1, line 12 - line 14 page 4, line 1 - line 10 page 11, line 7 - line 26 page 12, line 8 - line 11 page 13, line 20 - line 24 page 14, line 10 - line 22 example 4 table VII claims 1-8	1-3,6-9, 12-15

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INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/CA 01/00285

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 04887 A (FORBES MEDI TECH INC) 3 February 2000 (2000-02-03) page 1, paragraph 1 page 2, paragraph 4 -page 3, paragraph 2 page 9, paragraph 3 page 10, paragraph 2 page 12, paragraph 4 page 26, paragraph 3 page 27, paragraph 1 - paragraph 8 claims 1-5,10,11	1-4, 6-10, 13-17
A	US 5 244 887 A (STRAUB CARL D) 14 September 1993 (1993-09-14) abstract column 1, line 51 -column 2, line 52 column 4, line 25 -column 5, line 5 column 5, line 56 -column 6, line 44 claim 1	1-4, 6-10,13
P,X	WO 00 53176 A (MELEGARI PIERANGELO ;INTROINI CARLO (IT); UNI CI S R L (IT); BORGO) 14 September 2000 (2000-09-14) abstract page 2, line 8 - line 21 page 3, line 17 - line 31 page 5, line 33 -page 6, line 20 page 14, line 10 -page 15, line 4	1,15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-17 relate to a very large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Moreover, present claims 1-17 relate to a compounds and their therapeutic application which actually are not well-defined. The use of the definitions "a phytosterol and/or a phytostanol", "lipoic acid or analogues thereof", "derivatives thereof", "all saturated or hydrogenated phytosterols and all natural or synthesized forms and derivatives thereof" and "cardiovascular disease and its underlying conditions" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specified in the examples p. 12-13 and in the figures 1-3 (i.e. structures 5, 7 and 8), or to the combination of alpha-lipoic acid and the phytosterols and/or phytostanols fully specified in claims 2, 4, 8, 10 and the diseases relating to cardiovascular disease specified in the description (p. 6, par. 2), namely atherosclerosis, hypercholesterolemia, hyperlipidemia, hypertension and thrombosis, type II diabetes, dementia, Alzheimer's disease, aging, cancer.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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